



# The Role of Transocular Ultrasound in the Assessment of Neurotoxicity-Related Encephalopathy in Mushroom Poisoning

Fethi Gül<sup>1</sup> , İsmet Sayan<sup>2</sup> , Hüseyin Arıkan<sup>2</sup> , Sinan Karacabey<sup>3</sup> , Mustafa Kemal Arslantaş<sup>4</sup> , İsmail Cinel<sup>5</sup> 

<sup>1</sup>Department of Anaesthesiology and Reanimation, Marmara University Pendik Training and Research Hospital, İstanbul, Turkey

<sup>2</sup>Department of Pulmonary and Critical Care Medicine, Marmara University School of Medicine, İstanbul, Turkey

<sup>3</sup>Department of Traumatology and Emergency Medicine, Marmara University School of Medicine, İstanbul, Turkey

<sup>4</sup>Department of Anaesthesiology and Reanimation, Marmara University School of Medicine, İstanbul, Turkey

<sup>5</sup>Department of Anaesthesiology and Reanimation, Division of Critical Care Medicine, Marmara University School of Medicine, İstanbul, Turkey

*Cite this article as:* Gül F, Sayan İ, Arıkan H, Karacabey S, Arslantaş MK, Cinel İ. The Role of Transocular Ultrasound in the Assessment of Neurotoxicity-Related Encephalopathy in Mushroom Poisoning. *Turk J Anaesthesiol Reanim* 2020; 48(1): 62-7.

## Abstract

**Objective:** Mushroom poisonings can lead to life-threatening organ dysfunctions and neurotoxicity-related encephalopathy. This study aimed to detect increased intracranial pressure by measuring optic nerve sheath diameter (ONSD) ultrasonographically and to determine its association with clinical and laboratory parameters.

**Methods:** In this prospective case-control study, we evaluated the patients aged above 18 years who presented to the emergency department with mushroom poisoning. Vital signs, clinical and laboratory parameters and ONSD of both eyes measured with transocular ultrasound were noted at initial admission and the 24th hour.

**Results:** We measured ONSD in 26 cases with mushroom poisoning and 26 healthy volunteers. Baseline ONSD measurements of the poisoning group were significantly higher than those of the control group ( $5.94 \pm 0.73$  vs.  $4.11 \pm 0.64$ ,  $p < 0.0001$ ). ONSD values significantly regressed at 24th hour compared with the baseline measurements in the poisoning group ( $5.94 \pm 0.73$  vs.  $5.06 \pm 0.56$ ,  $p < 0.001$ ). The ONSD values were significantly higher in patients who had a clinical picture of encephalopathy compared with patients who didn't have ( $6.05 \pm 0.72$  vs.  $4.36 \pm 1.03$ ,  $p < 0.001$ ). No significant deterioration was observed in ammonium levels, hepatic and renal functions of the patients.

**Conclusion:** We detected increased ONSDs in patients with mushroom poisoning compared with those in the control healthy volunteers. Our findings suggest that ONSD, measured by ultrasonography, may be safely and effectively used to diagnose transient encephalopathy associated with neurotoxicity.

**Keywords:** Encephalopathy, mushroom poisoning, neurotoxicity, transocular ultrasound

## Introduction

Mushroom poisonings mostly appear in the autumn. Most of the poisonings lead to minor gastrointestinal findings, but life-threatening complications are seen in patients with a serious course (1). Detecting the true incidence of mushroom poisonings is difficult because the cases are frequently not reported. Nevertheless, 83,140 cases of mushroom poisoning have been detected in the US between 2001 and 2011; and 64,534 (77.6%) of them were seen in children (2).

Depending on the type of the mushroom consumed, symptoms begin within 6 h, but symptoms may also be seen later on (3, 4). Acute symptoms are predominantly related to gastrointestinal and central nervous system such as vomiting, abdominal pain, diarrhea, hallucinations, lightheadedness, drowsiness and headache. Later symptoms may include severe diarrhea, acute renal failure, a severe hepatic failure that may even lead to transplantation, and central nervous system manifestations such as stupor and coma (5).

Treatment of patients presenting with mushroom poisoning is symptomatic, and these patients must be followed-up for pathologies that may develop (6). Blood workup yields easy, fast and objective data for risk of developing hepatic and renal failures. Neurological examination is used to diagnose encephalopathy, and high-cost invasive methods are used to diagnose and follow increased intracranial pressure (ICP) (7, 8).

The optic nerve is a part of the central nervous system and is surrounded by the dural sheath. This sheath also enlarges as a reflection of ICP. It is possible to demonstrate the changes in the diameter of the nerve sheath using transocular ultrasound. Previously, many studies have addressed the correlation between the nerve sheath diameter and invasively measured ICP increase (9-11). Measurement of the optic nerve sheath diameter (ONSD) with ultrasound has been detected to have high sensitivity and specificity to demonstrate ICP; these measurements have been established to be safe when compared with images obtained with magnetic resonance imaging (12, 13).

This study aimed to evaluate the association of ONSD measured with transocular ultrasonography in patients with mushroom poisoning with clinical and laboratory parameters and its change by time.

## Methods

### Study population

We performed prospective case-control study for mushroom poisoning cases in patients aged above 18 years who presented to Pendik Research and Training Hospital between September and December 2017 after approval from Marmara University, Clinical Research Ethics Committee (09.2018.104). Written informed consent was obtained from all patients. We excluded individuals who were younger than 18 years, had an intracerebral space-occupying lesion, encephalitis, meningitis, diseases of the optic nerve, Graves' disease and previous cerebrovascular disease and who were pregnant. The encephalopathy was manifested by an altered mental state with a depressed level of consciousness ranging from confusion to coma. We recorded vital signs, clinical and laboratory parameters [prothrombin international normalised ratio (INR), alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH)] and ONSD of both eyes measured with transocular ultrasound at initial admission and the 24<sup>th</sup> hour.

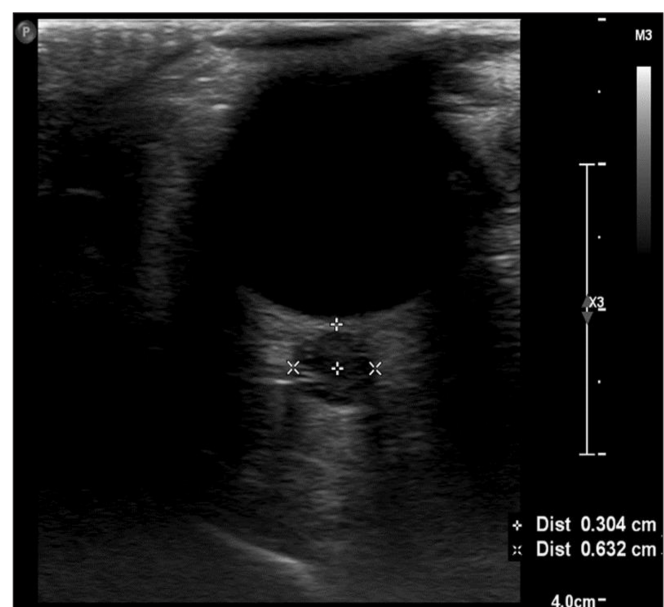
### Transocular ultrasonography

All ultrasonographic measurements were performed using Philips EPIQ 7 Ultrasound system (Philips Healthcare, Inc., Andover, MA, USA). An intensive care specialist experienced in ultrasonography performed the measurements. Vertical

and horizontal diameters of both optic nerves were measured at the supine position while eyelids were closed. Optic nerve could be visualised by locating the probe at the upper and lateral side of the upper eyelid (12, 13). ONSD was measured 3 mm behind retina by using B-mode 7.5 MHz linear probe (Figure 1). Measurements were performed for both eyes, and the mean values were recorded.

### Statistical analysis

A post-hoc power analysis revealed that on the basis of the mean, between-groups comparison effect size (GPower 3.1 software) observed in this study ( $d=2.66$ ), a number of approximately 10 would be needed to obtain statistical power at the recommended 0,95 level using Cohen's (1988) criteria. The Shapiro-Wilk test was performed for normality distribution of numerical variables. Continuous parametric variables were presented as the mean and standard deviation and compared using the Student t-test, whereas continuous nonparametric variables were presented as the median and percentiles [25<sup>th</sup>–75<sup>th</sup>] and compared with the Mann-Whitney U test. Categorical variables between the groups were measured by 2×2 tables using Pearson's chi-square test and Fisher's exact test. Paired samples t-test and independent samples t-test were used to compare continuous variables independent groups and continuous variables between two independent groups, respectively. Results were considered statistically significant when the p value was below 0.05. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences version 23.0 software (IBM SPSS Corp.; Armonk, NY, USA).



**Figure 1. Two-dimensional ocular ultrasonography for measurement of optic nerve sheath diameter. ONSD was measured 3 mm behind the retina, along with the axis of the optic nerve that corresponds to the distance between the two external parts**

## Results

ONSDs were measured in 26 patients whose poisoning symptoms started >6 h from the consumption of mushroom. Also, 26 healthy volunteers were included as the control group. Demographic characteristics of the patients are shown in Table 1. The mean age of the patients presented with mushroom poisoning was 44.27±0.73 years, and of the control group was 42.65±5.29 years.

In the poisoning group, encephalopathy was present in 17 patients (68%) at the time of presentation. After the recommendation of nephrology department, prophylactic haemodialysis was performed to 14 patients (53.5%) irrespective of encephalopathy (Table 2). Clinical findings improved to normal in all patients with encephalopathy at the 24<sup>th</sup> hour. Two patients were intubated and admitted to the intensive care unit because of accompanying respiratory distress. We measured ammonia levels and liver function tests in all patients, and they were within normal limits.

	Group 1 (n=26)	Group 2 (n=26)	p
Age (years)	45 [27–54]	44 [38–46]	0.912
Gender (M/F)	14 / 12	7 / 19	0.089

M: male; F: female

	Yes	No
Encephalopathy	17	8
Acute kidney injury	0	26
GIS symptoms	1	25
Needs for dialysis	14	12

GIS: gastrointestinal symptoms

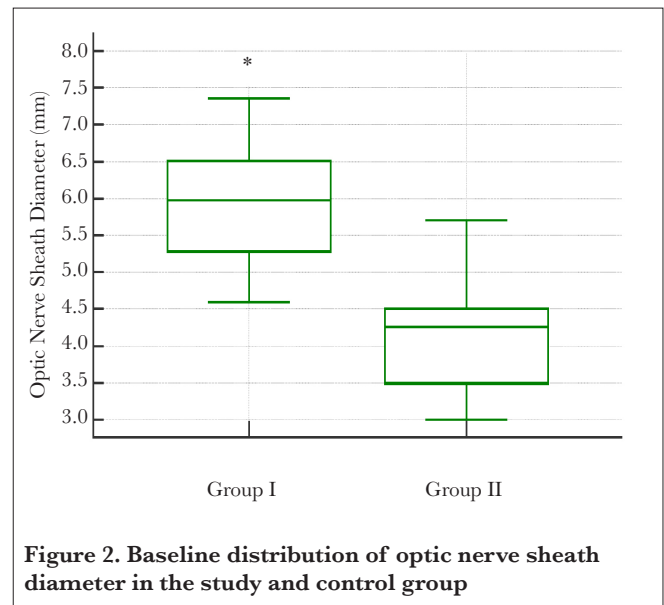
Parameter	Mean±SD	Normal values
INR	1.32±0.32	0.8–1.2
Ammoniac (mmc)	28.38±12.84	11–51
Bilirubin (mg dL <sup>-1</sup> )	0.57±0.31	0–1.3
ALT (U L <sup>-1</sup> )	22.73±13.86	10–40
AST (U L <sup>-1</sup> )	25±10.20	10–37
ALP (U L <sup>-1</sup> )	64.81±18.14	50–142
GGT (U L <sup>-1</sup> )	23.77±22.08	7–49
LDH (U L <sup>-1</sup> )	241.19±79.01	0–248

INR: prothrombin international normalised ratio; ALT: alanine aminotransferase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase

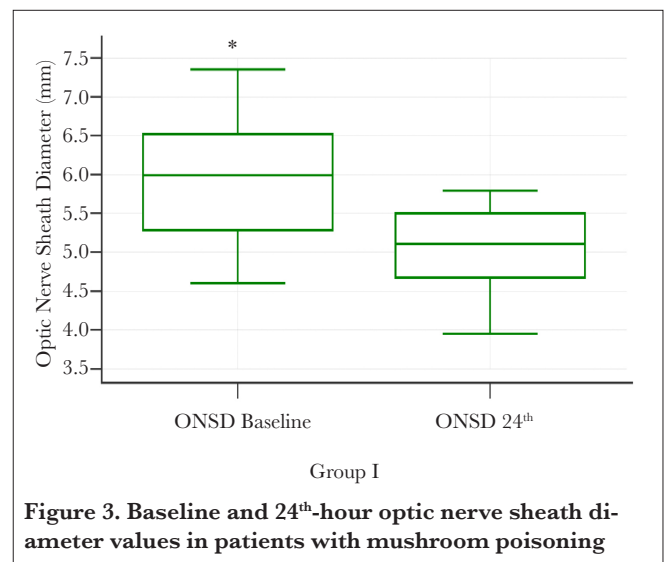
Distribution of laboratory parameters used in this study is given in Table 3.

Baseline ONSD measurements of the poisoning group were significantly higher than those of the control group (5.94±0.73 vs. 4.11±0.64, p<0.0001) (Figure 2). ONSDs were significantly lower than basal values at the 24th-hour measurements in the poisoning group (5.94±0.73 vs. 5.06±0.56, p<0.001) (Figure 3).

Comparison of poisoning patients who had or did not have encephalopathy at initial presentation demonstrated that ONSDs of the patients with encephalopathy were higher than in the patients who did not have encephalopathy (6.05±0.72 vs. 4.36±1.03, p<0.001) (Table 4).



**Figure 2. Baseline distribution of optic nerve sheath diameter in the study and control group**



**Figure 3. Baseline and 24<sup>th</sup>-hour optic nerve sheath diameter values in patients with mushroom poisoning**

	The presence of encephalopathy		p
	Yes (n=17)	No (n=8)	
ONSD baseline (mm)	6.05±0.72	4.36±1.03	<0.0001
ONSD: optic nerve sheath diameter			

## Discussion

In our study, we detected larger ONSDs in patients who presented to emergency department with mushroom poisoning compared with those in the healthy volunteers of control group. We detected that the ONSD was associated with encephalopathy, and the diameter of the optic nerve sheath declined at the 24<sup>th</sup> hour with regression of the clinical picture of encephalopathy. Our findings suggest a significant association between ultrasonographically measured ONSDs and clinical findings after other causes of encephalopathy are excluded and without any change in laboratory findings of patients with mushroom poisoning. Therefore, our study is the first study in the literature on this specific issue.

Mushrooms are collected from nature and consumed as food. Poisonings are frequent in spring and autumn (14). Symptoms appear approximately within 3 h in mushrooms with short symptom-onset and within 6–24 h in mushrooms with longer symptom-onset. Early symptoms of mushroom poisoning are abdominal pain, nausea, vomiting, diarrhoea, hypotension and electrolyte imbalance. Prognosis is generally good in mushroom poisonings that give symptoms at an early period (within the first 6 h). Up to 90%–95% of late-onset cases are reported to be fatal (5). In this period, direct effects of fungal toxins, hypovolemia due to fluid loss or acute kidney damage due to hepatic failure may occur. Encephalopathy, coagulopathy, renal failure and progressive hepatic failure with acidosis may occur due to hepatotoxic effects (3, 4). Activated charcoal should be given for all cases with mushroom poisoning to prevent absorption of the toxins. Aggressive intravenous fluid treatment should be applied and, if present, electrolyte imbalances should be corrected (6). Chang first defined hemoperfusion treatment, and mortality is shown to be decreased 50% by hemoperfusion. Hemoperfusion also rapidly decreases toxin-related encephalopathy (15). Hepatic transplantation is the most effective treatment for patients who develop fulminant hepatic failure. As true for other causes of fulminant hepatic failure, hepatic support systems may be used in mushroom poisonings to gain time pending liver transplantation (16). In our study, aggressive fluid and electrolyte treatments were started for all patients after the diagnosis and gastric lavage, and activated charcoal was applied to all patients. Fulminant hepatic

failure didn't develop in any of the patients, but the clinical picture of encephalopathy was present in 17 patients in our study. Although no patients develop acute renal damage, hemoperfusion with carbon filter was applied to 14 patients considering their clinical conditions. Any mushroom that causes fulminant hepatic failure or that is epileptogenic may be associated with encephalopathy. However, an encephalopathic syndrome without an associated hepatic failure may be seen as in our patients (17). Before considering toxins as the causes of encephalopathy uraemia, ethylism and poisonings other than mushrooms should be considered and excluded.

Intracranial pressure is a sign of numerous neurological disorders, and delay in diagnosis and treatment can have devastating consequences. Guidelines recommend targeting ICP<20–25 mmHg during follow-up for traumatic brain injury and other acute brain injuries (18, 19). Invasive methods such as an intraparenchymal probe or intraventricular catheter are standard methods for invasive ICP follow-up. However, because of their invasiveness, they carry risks such as bleeding and infection (20). The sheath surrounding the optic nerve is actually a continuation of dura, and subarachnoid space extends through the optic nerve within subarachnoid space. Therefore, an increase in ICP is conducted to optic nerve head, and it causes optic disc swelling and papilloedema. Development of papilloedema may take several hours to several days, and human studies have demonstrated that increased ICP was due to swelling of the optic nerve sheath within seconds (21). Ultrasonographic measurement of the optic nerve sheath at a certain distance from the retina is a noninvasive method to detect increased ICP especially in patients with traumatic brain injury or intracranial haemorrhage that has been evaluated in many studies (9, 10, 22). In one of the largest studies on this topic, ultrasonographically measuring ONSD larger than 0.48 cm predicted ICP > 20 mmHg with a 96% sensitivity and 94% specificity (12). A limited number of studies have investigated increased ICP due to causes other than trauma, tumour or haemorrhage. To evaluate cerebral oedema due to diabetic ketoacidosis, ultrasonographic evaluation may be used instead of examination for papilloedema because it appears earlier. However, it is suggested to be more effective to detect patients under risk for cerebral oedema development rather than for monitorisation (23). Studies have been performed that used ONSD for diagnosis and follow-up of altitude sickness. However, a consensus has been reached about the limitation of this method for diagnosis of altitude sickness because of the marked variability in ONSD measurements (24–26). Also, literature suggested that ultrasonographic ONSD follow-up may be safely used for preoperative management of hepatic encephalopathy in patients with acute hepatic failure requiring hepatic transplantation for whom invasive ICP monitorisation can't be done because of coagulopathy (27, 28).



The ONSD measurements have some limitations. In our study, an intensivist who was experienced in ultrasonography performed the measurements. A certain time will be needed for a clinician new to this technique to obtain adequately safe and reproducible measurements. Moreover, the technique is adequate to demonstrate static changes in ICP but not appropriate for continuous monitoring and follow-up of acute and dynamic changes.

In this study, it was observed that independent from hepatic and renal dysfunctions, ONSD increased in cases that develop clinical encephalopathy associated with mushroom poisonings and the measurements regressed concurrently with clinical improvement at the 24<sup>th</sup> hour.

## Conclusion

Our findings suggest that in the aforementioned patient group, ONSD measured with ultrasonography in addition to laboratory workup may be used safely and effectively to diagnose transient encephalopathy associated with neurotoxicity and to follow-up its progression.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Marmara University (09.2018.104).

**Informed Consent:** Written informed consent was obtained from all patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – F.G., İ.C.; Design – F.G., İ.C.; Analysis and/or Interpretation – F.G., İ.S., H.A., S.K., M.K.A., İ.C.; Writing Manuscript – İ.C., F.G., H.A.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

- Diaz JH. Evolving global epidemiology, syndromic classification, general management, and prevention of unknown mushroom poisonings. *Crit Care Med* 2005; 33: 419-26. [\[CrossRef\]](#)
- Hatten BW, McKeown NJ, Hendrickson RG, Horowitz BZ. The Epidemiology of Mushroom Ingestion Calls to US Poison Control Centers: 2001-2011. *Clin Toxicol* 2012; 50: 274-720.
- Berger KJ, Guss DA. Mycotoxins revisited: Part I. *J Emerg Med* 2005; 28: 53-62. [\[CrossRef\]](#)
- Berger KJ, Guss DA. Mycotoxins revisited: Part II. *J Emerg Med* 2005; 28: 175-83. [\[CrossRef\]](#)
- Goldfrank LR. Mushrooms. In: Hoffman RS, Howland MA, Lewin NA, Nelson LS, Goldfrank LR, editors. *Goldfrank's Toxicologic Emergencies*. 9 ed. New York: McGraw-Hill; 2011. p. 1522-36.
- Diaz JH. Syndromic diagnosis and management of confirmed mushroom poisonings. *Crit Care Med* 2005; 33: 427-36. [\[CrossRef\]](#)
- Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. *Am J Med* 2003; 114: 188-93. [\[CrossRef\]](#)
- Gasco J, Rangel-Castilla L, Franklin B, Thomas PG, Patterson JT. State-of-the-art management and monitoring of brain edema and intracranial hypertension in fulminant hepatic failure. A proposed algorithm. *Acta Neurochir Suppl* 2010; 106: 311-4. [\[CrossRef\]](#)
- Geeraerts T, Launey Y, Martin L, Pottecher J, Vigue B, Duranteau J, et al. Ultrasonography of the optic nerve sheath may be useful for detecting raised intracranial pressure after severe brain injury. *Intensive Care Med* 2007; 33: 1704-11. [\[CrossRef\]](#)
- Kimberly HH, Shah S, Marill K, Noble V. Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure. *Acad Emerg Med* 2008; 15: 201-4. [\[CrossRef\]](#)
- Soldatos T, Karakitsos D, Chatzimichail K, Papatheasios M, Gouliamos A, Karabinis A. Optic nerve sonography in the diagnostic evaluation of adult brain injury. *Crit Care* 2008; 12: R67. [\[CrossRef\]](#)
- Rajajee V, Vanaman M, Fletcher JJ, Jacobs TL. Optic nerve ultrasound for the detection of raised intracranial pressure. *Neurocrit Care* 2011; 15: 506-15. [\[CrossRef\]](#)
- Bauerle J, Schuchardt F, Schroeder L, Egger K, Weigel M, Harloff A. Reproducibility and accuracy of optic nerve sheath diameter assessment using ultrasound compared to magnetic resonance imaging. *BMC Neurol* 2013; 13: 187. [\[CrossRef\]](#)
- Eren SH, Demirel Y, Ugurlu S, Korkmaz I, Aktas C, Güven FMK. Mushroom poisoning: retrospective analysis of 294 cases. *Clinics* 2010; 65: 491-6. [\[CrossRef\]](#)
- Bartels O. Mushroom poisoning. New possibilities for treatment. *Fortschritte der Medizin*. 1976; 94: 539-44.
- Karvellas CJ, Tillman H, Leung AA, Lee WM, Schilsky ML, Hameed B, et al. Acute liver injury and acute liver failure from mushroom poisoning in North America. *Liver Int* 2016; 36: 1043-50. [\[CrossRef\]](#)
- Graeme KA. Mycetism: a review of the recent literature. *J Med Toxicol* 2014; 10: 173-89. [\[CrossRef\]](#)
- Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, et al. Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. *J Neurotrauma* 2007; 24(Suppl 1): S37-44. [\[CrossRef\]](#)
- Hemphill JC, 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2015; 46: 2032-60. [\[CrossRef\]](#)
- Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, et al. Guidelines for the management of

- severe traumatic brain injury. VII. Intracranial pressure monitoring technology. *J Neurotrauma* 2007; 24(Suppl 1): S45-54. [\[CrossRef\]](#)
21. Helmke K, Hansen HC. Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension II. Patient study. *Pediatr Radiol* 1996; 26: 706-10. [\[CrossRef\]](#)
  22. Moretti R, Pizzi B, Cassini F, Vivaldi N. Reliability of optic nerve ultrasound for the evaluation of patients with spontaneous intracranial hemorrhage. *Neurocrit Care* 2009; 11: 406-10. [\[CrossRef\]](#)
  23. Szymgel Ł, Kosiak W, Zorena K, Myśliwiec M. Optic Nerve and Cerebral Edema in the Course of Diabetic Ketoacidosis. *Curr Neuropharmacol* 2016; 14: 784-91. [\[CrossRef\]](#)
  24. Keyes LE, Paterson R, Boatright D, Browne V, Leadbetter G, Hackett P. Optic nerve sheath diameter and acute mountain sickness. *Wilderness Environ Med* 2013; 24: 105-11. [\[CrossRef\]](#)
  25. Strapazzon G, Brugger H, Dal Cappello T, Procter E, Hofer G, Lochner P. Factors associated with optic nerve sheath diameter during exposure to hypobaric hypoxia. *Neurology* 2014; 82: 1914-8. [\[CrossRef\]](#)
  26. Fagenholz PJ, Gutman JA, Murray AF, Noble VE, Camargo CA, Jr, Harris NS. Optic nerve sheath diameter correlates with the presence and severity of acute mountain sickness: evidence for increased intracranial pressure. *J Appl Physiol* (1985) 2009; 106: 1207-11. [\[CrossRef\]](#)
  27. Kim YK, Seo H, Yu J, Hwang GS. Noninvasive estimation of raised intracranial pressure using ocular ultrasonography in liver transplant recipients with acute liver failure -A report of two cases. *Korean J Anesthesiol* 2013; 64: 451-5. [\[CrossRef\]](#)
  28. Krishnamoorthy V, Beckmann K, Mueller M, Sharma D, Vavilala MS. Perioperative estimation of the intracranial pressure using the optic nerve sheath diameter during liver transplantation Liver Transpl 2013; 19: 246-9. [\[CrossRef\]](#)